DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Kathleen D. Jaeger, Esq.
McKenna & Cuneo, L.L.P.
1900 K Street, N.W.
Washington, D.C. 20006

Re: Docket No. 99P-0189/CP1

Dear Ms. Jaeger:

This responds to your citizen petition dated January 29, 1999, requesting that the Food and Drug Administration (FDA) designate Levlite (manufactured by Berlex Laboratories) as an alternate reference listed drug for ethinyl estradiol 0.02 milligram (mg)/levonorgestrel 0.1 mg tablets, in addition to Alesse (manufactured by Wyeth-Ayerst). For the reasons stated below, your request is granted.

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an approved abbreviated new drug application (ANDA). To gain approval, the ANDA must show, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product has the same active ingredient(s) in the same strength, that its labeling is essentially identical, and that it is bioequivalent. The specific approved drug product to which an ANDA refers is known as the *reference listed drug*.

FDA's policy on the designation of reference listed drugs is described in the preamble to the final rule establishing the requirements for ANDA's, published in the *Federal Register* of April 28, 1992 (57 FR 17950, 17958):

> . . . FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

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FDA has examined the issues presented in your petition and has determined that the grounds set forth in your petition permit designation of Levlite as an alternate reference listed drug under FDA policy. As stated in your petition, FDA will designate a second reference listed drug when two innovator products are bioinequivalent to each other, as is the case here with Alesse and Levlite. Furthermore, the Agency has determined that it would not be in the public interest to foreclose approvals of ANDAs that wish to cite Alesse as the reference listed drug. Accordingly, the FDA will designate Levlite, in addition to Alesse, as a reference listed drug in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*).

FDA is aware that the presence of two reference listed drugs in the *Orange Book* may create the potential for some confusion and inappropriate substitution. If generic ethinyl estradiol 0.02 mg/levonorgestrel 0.1 mg tablet drug products are approved, FDA will take appropriate steps to make it clear in the *Orange Book* that Alesse and Levlite are not therapeutically equivalent to each other, and that a generic drug product that is therapeutically equivalent to either Alesse or Levlite is not therapeutically equivalent to the other.

Sincerely yours,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research